to develop the foundation for good working relationships between physicians and nurse practitioners.[12] Such opportunities would enable both groups of students to learn about one another's knowledge, skills, and perspectives, thus creating a foundation for developing the trust and respect essential to effective collaboration between nurse practitioners and physicians.

There is some reason to be sanguine. The results of a recent study of nurse practitioners and physician assistants providing primary care services in HMOs and multispecialty groups suggest that nurse practitioners and physician assistants in these settings have collegial relationships with physicians (P. D. Jacobson, L. E. Parker, I. D. Coulter, working paper, RAND Corporation).

The article by Anderson and colleagues offers a launching pad for at least three further lines of research that would address the degree to which remaining barriers to nurse practitioner practice in California impede efforts to expand access to care, improve the quality of care, and contain health care costs; the effects of restrictions on prescribing authority and reimbursement on the quality and range of health care services nurse practitioners provide in California; and the perceptions of both physicians and nurse practitioners regarding their evolving practice relationships, regulatory realities, and suggestions for improvement.

As systems move to more integrated and managed arrangements for providing health care, they will inevitably raise more questions about who can provide accessible and high-quality services for the lowest costs. The laws and regulations that health care professionals have used to protect the public and their scopes of practice will face important pressures to transform. The resulting tension will play out not only between nurse practitioners and physicians, but between registered nurses and unlicensed assisted personnel, pharmacists and pharmacist technicians, and dentists and dental hygienists. It is our challenge to make this tension creative.

The best reaction to this from the organized professions would be to understand the perspective and value that each brings to providing care and to agree on the broadest possible arena of shared practice, rather than the narrowest. Ultimately, this must lead to innovative and long-term collaborations in practice and regulation that protect and promote the public's health by the most efficient and rational means possible.

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Parkinson's Disease—A Progress Report

THE SHAKING PALSY described in 1817 by James Parkinson, a general practitioner working in London, is a common neurodegenerative disorder that increases in prevalence with advancing age and is associated with an increased risk of death.[1] It results from the progressive loss of dopaminergic neurons in the substantia nigra of the midbrain, as a consequence of which the striatal concentration of the neurotransmitter dopamine is reduced. Dopaminergic and nondopaminergic cells in other regions are also affected, but loss of the striatonigral projection neurons is the most conspicuous pathologic finding. The cause of this cell loss is obscure. The occurrence of a similar disorder in humans with exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine suggests that toxic exposure is responsible for Parkinson's disease, but no likely exogenous toxin has been identified. An endogenous toxin may be involved. There is evidence that oxidative stress resulting from the metabolism of dopamine is increased,[2] with the formation of free radicals that lead to DNA damage, lipid peroxidation, and cell death. Dopamine is catabolized by monoamine oxidase to 3,4-dihydroxyphenylacetic acid with the generation of hydrogen peroxide, and this in turn may lead to the generation of hydroxyl free radicals. These radicals may be injurious to dopaminergic neurons if the normal protective mechanisms are impaired. Factors influencing the metabolism and distribution of dopamine may therefore be important in the pathogenesis of the disease[2] and are currently under study. There is no evidence, however, that vitamin E, a scavenger of free radicals, exerts any protective effect in patients with Parkinson's disease when taken in daily doses of 2,000 units, although the extent to which it pen-

etrates into the brain is unclear.

The role of heredity in the development of Parkinson's disease is also being reexamined. Early clinical studies of monozygotic or dizygotic twins suggested that genetic factors were not important, but recent studies involving positron-emission tomography have shown the asymptomatic twins of affected patients to have a higher frequency of abnormalities of dopaminergic nigrostriatal function than previously appreciated.[3,4] Work is in progress in several laboratories to identify any genes contributing to the development of the disease.

Over the past decade, it has become clear that the basal ganglia operate as part of functionally distinct parallel circuits that involve the thalamus and cerebral cortex. Several different areas of the cerebral cortex project to the neostriatum, from which there are pathways to the substantia nigra pars reticularis and medial globus pallidus either directly (involving γ-aminobutyric acid [GABA] as neurotransmitter) or indirectly (using GABA-ergic and glutamatergic projections) by the lateral globus pallidus and subthalamic nucleus.[5] The substantia nigra pars reticularis and medial globus pallidus are the main output structures of the basal ganglia and project to the thalamus and thus to the cortex. The precise role of the basal ganglia in motor function remains to be established. It seems, however, that the loss of striatal dopamine results in increased neuronal activity in the pallidal output of the basal ganglia. This, in turn, results in an increased inhibition of thalamic cells projecting to the frontal cortex and thus to reduced motor activity.[5] These concepts have suggested several new therapeutic strategies, which I will discuss.

Treatment of the disorder remains controversial despite the enormous advances of the past quarter century. Elsewhere in this issue of the *Journal*, Don Ng, MD, provides an account for primary care physicians of the general therapeutic approach.[6] It is perhaps worth reiterating that the role of selegiline (a monoamine oxidase B inhibitor) as a neuroprotective agent is uncertain. It is not clear whether selegiline slows disease progression, and studies aimed at clarifying this point have yielded ambiguous or conflicting results. The decision to prescribe this agent, therefore, remains an individual one, requiring the possible but uncertain benefit of treatment to be balanced against the high cost involved and safety concerns fueled by a recent report of increased mortality associated with the use of selegiline.[7] Other monoamine oxidase B inhibitors, such as lazabemide, are undergoing clinical evaluation for any neuroprotective effect, and these studies may provide further guidance for practitioners. It must also be emphasized that complete agreement is lacking on the optimal time and manner for introducing dopaminergic therapy. Many neurologists prefer to start dopaminergic therapy with one of the dopamine agonists rather than with a levodopa-carbidopa combination (Sinemet) because the agonists do not require enzymatic conversion to an active agent and are not metabolized by oxidation, with the generation of free radicals. This approach has the advantage of delaying the development of such side effects as response fluctuations. Ultimately, however, most patients will require combination treatment with Sinemet and a dopamine agonist for benefit. Several new dopamine agonists are undergoing clinical trials, and new methods of administering them are being explored in the hope of obtaining a steadier clinical response.

Novel symptomatic agents are also being evaluated. Selective inhibitors of catechol-*O*-methyltransferase—an enzyme involved in one pathway for the metabolic breakdown of levodopa—may enhance the benefits of levodopa therapy. There are theoretical grounds for thinking that glutamate antagonists will also be helpful in treating parkinsonism by reducing the activity of the subthalamic nucleus, which is driven by glutamatergic output of the motor cortex, and of the glutamatergic connections of the subthalamic nucleus with the substantia nigra and medial globus pallidus. Various neurotrophic factors have been shown in animals to influence dopaminergic nigrostriatal cells, and the development of effective systems for delivering them to the brain may eventually revolutionize the treatment of Parkinson's disease.

Until more effective pharmacologic therapies are developed, operative treatment based on the newly recognized motor circuitry of the basal ganglia should be considered for patients with classic Parkinson's disease who are becoming increasingly disabled despite dopaminergic therapy or who have intolerable side effects of treatment, such as response fluctuations or severe dyskinesias. Pallidotomy (ablation of the globus pallidus) is performed for bradykinesia, rigidity, or postural instability, and thalamotomy for tremor. Other experimental invasive procedures involve high-frequency stimulation of the subthalamic nucleus, thalamus, or globus pallidus, but the mechanisms involved and long-term results of these approaches are unknown.[8] The cerebral transplantation of adrenal medullary or fetal mesencephalic tissue also remains experimental, is undertaken in only a few specialized centers, and has yielded mixed results.

Recent experimental work has provided intriguing fresh insights into an ancient malady and suggested new therapeutic strategies that hold promise for improving the clinical deficit that occurs in Parkinson's disease. Further work is necessary to ensure that the promise becomes a reality.

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A Guide of the Perplexed—Assisted Suicide

AS SOON AS people learn I work in medical ethics, they ask, "What do you think of Jack Kevorkian?" Many physicians, I am sure, get the same question. Some questioners hope to hear the Michigan pathologist praised as a brave hero, others expect him to be condemned as a base buffoon. My answer is that Jack Kevorkian is too sure of himself, too certain of his cause. In the matter of euthanasia and assisted suicide, I think a humble perplexity is the only moral attitude. Melinda Lee, MD, Linda Ganzini, MD, and Kenneth Brummel-Smith, MD, demonstrate some of that perplexity in their article, "When Patients Ask About Assisted Suicide," elsewhere in this issue of the *Journal*.[1] Writing from the only state in the Union that has legally authorized the prescription of lethal doses of medication for terminally ill patients who so request (implementation of which is currently blocked by an injunction), they report that Oregon physicians were "almost evenly split" on the issue of physician-assisted suicide, and they interpret the close vote by Oregon's electorate as a sign of "ambivalence and diverse motives among the voters." My colleagues and I found the same division among Washington State physicians, where an equally close vote disapproved what Oregon voters had narrowly approved.[2] Although a split opinion by physicians and a split vote by the public can mean that those on either side are passionately committed to their positions, it can also suggest that many on the fence just slipped off on one side or another, still unsure which side is right or wrong. Split public opinions may demonstrate split private opinions, and the 48-to-52 split of a poll can echo in the conscience of a person. This perplexity may or may not be empirical fact, but it should be the moral attitude to take in the face of this momentous shift in the ethics of medicine.

One of medicine's greatest physicians, Moses Maimonides of 12th century Cordoba and Cairo, wrote the book *The Guide of the Perplexed*.[3] He wrote not as a physician but as a philosopher and examined with exquisite care such deep questions as the creation of the world and the immortality of the soul. He demonstrated that human reason can clarify much about these questions but is powerless to resolve them. Perplexity is the proper stance of reason before mysteries. Religious faith alone closes the questions. The advice of the great Maimonides is worth recalling in this modern debate. Whereas some physicians adhere to a religious faith that will close the question of assisting death, many others, even the sincerely religious, will not find the final answer. Many physicians will find only the ambiguous conscience that can see both good and bad reasons on both sides of the debate.

Physicians are rarely philosophers and almost never great philosophers like Maimonides. They cannot merely meditate on these problems. They are forced to respond to patients who inquire about their stance and about their willingness to assist. They are now and increasingly will be forced to decide. If they incline toward a yes answer, they will have to learn, as Lee and associates suggest, much more about this new facet of patient care. The psychology of the seriously ill will have to be better understood. The highly subjective quality and quantity of suffering will have to be carefully assessed. The pharmacology of "overdosing" that physicians have assiduously avoided will have to be mastered. The technicalities of the law and regulations that will inevitably surround this practice will have to be correctly interpreted. Kevorkian has hardly been an exemplar for the competent physician willing to assist patients to die.

Even those who incline to the yes side will be faced with agonizing decisions. Each state will have its own law and regulations, but the Oregon statute will serve as something of a model. At present, those who advocate legal authorization tend to avoid the broad formulations of the recent past. Physicians may hasten death only for those conscious and competent enough to ask for help. Further, under the Oregon model, they may only prescribe medication, not administer it. This is the safest legal formulation. Yet, it leaves physicians and families with painful problems. There will be persons whose terminal condition arrives suddenly and without prevision. Unable to ask, they will suffer for long periods. Others will suffer but not be terminal in any technical sense. Some who can request help may be unable to self-administer the prescribed medication. Willing physicians will be constantly tempted to move beyond the law's safe line.

Those physicians who incline to the no side will not be able to shelter themselves from the paradoxes. They may find that patients for whom they have long cared seek help in dying that they cannot conscientiously offer. Such a conclusion to a caring relationship may pain everyone. Unwilling physicians may even feel obliged to inform every new patient of his or her stance long before any situation calls for a decision. Unwilling physicians may find themselves exiles in a health care culture where a willing compliance with requests for assisted suicide is taken for granted.

Perhaps the most perplexing part of this problem will come for those philosophically minded physicians who have thought through the ethics of this matter. There are many arguments in the literature, from the invocation of the Hippocratic Oath to the anticipation of the "slippery slope." Some physicians have considered these arguments closely and evaluated their strengths and weaknesses as justifications for acting or refraining. One of the most persuasive arguments on the side of hastening death was offered by Howard Brody, MD, who argues that the presumptive duty to assist a patient to die easily derives